PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE **Ph.D. DEGREE** IN THE SUBJECT OF **CHEMISTRY**

Title of the topic	:	**"Design, Synthesis and Pharmacological Evaluation of Nitrogen-Containing Bioactive Molecules"**
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Basic Qualification	:	M.Sc. Organic Chemistry
In the case of Ph.D. student Year of Passing of PET/ NET/ SET/ M.Phil./ GPAT/ GATE (Teaching Experience)	:	SET, GATE
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Date of Superannuation/ Retirement of the Research Supervisor/Guide	:	31st July 2044
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Signature of the Head of the Department		

Date: 08/10/2021
14/10/2021

Signature of Head of College

Signature of Head/Director/
Principal Research Centre

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1. Title:

"Design, Synthesis and Pharmacological Evaluation of Nitrogen-Containing Bioactive Molecules"

2. Aims of the study:

To design and synthesize diversely functionalized Nitrogen-containing heterocycles, their structural investigations and evaluation of therapeutic potential *viz.* anti-inflammatory, antioxidant, anticancer and antimicrobial.

3. Objective of the study:

The objectives of the present studies are as follows:

- Designing and synthesis of Nitrogen-containing heterocycles employing simple and efficient methods.
- Structural investigations of the synthesized heterocyclic moieties by spectroscopic techniques.
- Therapeutic screening of the synthesized molecules.
- Molecular docking studies for the investigation of binding interactions.

4. Study Background (Literature Review) and significance of study

Heterocyclic compounds constitute the largest and most diverse family of organic compounds with chemical, biomedical, and industrial significance. They are an integral part of numerous natural products, such as vitamins, hormones, antibiotics, alkaloids, and herbicides. Heterocyclic compounds are normally classified according to the size of the heterocyclic ring and the nature and number of the heteroatoms. More than 85% of pharmaceuticals are heterocycles. The biological properties of heterocycles, in general, make them one of the prime interests of the pharmaceutical industry and biotechnology industries. The application of heterocycles provides a useful tool for the modification of solubility, lipophilicity, polarity, and hydrogen bonding capacity of biologically active agents, which results in the optimization of the ADME/Tox properties of drugs or drug candidates.

Nitrogen-containing heterocycles are an important and unique class of bioactive heterocyclic compounds. More than 75% of drugs approved by the FDA and currently available

in the market are nitrogen-containing heterocyclic scaffolds [1]. These molecules have received increasing attention over the past two decades. Many *N*-heterocyclic compounds that are broadly distributed in Nature, possess a wide range of physiological and pharmacological properties and are constituents of many biologically important molecules [2]. These nitrogen-containing heterocyclic molecules with distinct characteristics and applications have gained importance in the rapidly expanding fields of organic and medicinal chemistry [3]. Nearly 75% of unique small-molecule drugs contain a nitrogen heterocycle. Among them, phenanthridines, indoles, quinolines, isoquinolines, imidazopyridines, pyrazoles, thiazoles, etc. have gained considerable attention in organic synthesis, medicinal chemistry, and materials science.

Literature review

Recently, Vitaku and colleagues published a comprehensive compilation of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA-approved pharmaceuticals [4]. The *N*-heterocyclic skeletons feature significantly various classes of therapeutic applications and are used as the building blocks of a number of new drug candidates, due to the ability of the nitrogen atom to easily form hydrogen bonding with biological targets [5].

Significance of the Study

The utility of N-heterocyclic compounds is a hot topic in medicinal chemistry and chemical science, as can be seen in the list of nitrogen-containing clinical drugs. The exceptional role of nitrogen in variable interactions with biological targets broadens the scope of drug development.

5. National Status

Nitrogen heterocycles are among the most important structural classes of chemical substances, which are particularly well represented among natural products, biologically active structures, and medicinally relevant compounds. In light of the importance of these classes of compounds, their synthesis and biological evaluation have attracted much attention from national researchers. Dalip Kumar and his group constantly working on the synthesis and biological evaluation of various nitrogen heterocycles [6]. Bandgar et.al., also working on the diversity-oriented synthesis of nitrogen-based heterocycles and their anti-inflammatory and antioxidant evaluation [7].

6. International Status

Due to exhibiting diverse biological activities, nitrogen heterocyclic compounds have always been attractive targets to synthetic organic chemists around the globe. In 2014 Njardarson et al. published the first comprehensive analysis of nitrogen-based heterocycles. This analysis showed that indeed about 60% of small-molecule drugs contain N-based heterocycles as common architectural cores [8]. In 2018, Ramazani and co-workers presented the recent advances in nitrogen-based heterocycles as useful cancer chemotherapy agents [9].

7. Study Hypotheses

In light of the importance of nitrogen-based heterocycles, it is assumed that the synthesized nitrogen-containing heterocycles viz. pyrazole and imidazopyridine may acquire significant anti-inflammatory, antioxidant, and analgesic properties.

8. Study Rationale

Nitrogen heterocycles are well-documented for a broad array of activities. Especially fused nitrogen heterocycles are known to possess anticancer, antimicrobial, anti-inflammatory, antiepileptic, and antidepressant activities. Keeping these activities in view the present study was designed to synthesize novel small molecules based on nitrogen heterocycles and evaluate their pharmacological activities.

9. Research Methodology

To achieve the synthesis of designed target molecules, various methodologies are to be followed depending on the nature of the substrates. Considerable attention is being paid to minimizing the waste of chemicals and time and following the economically viable routes adopted in a research method. During the research work, various analytical methods have been adopted to purify and characterize the synthesized molecules.

The following steps are to be adopted to carry out the proposed research work:

1. Preparation of the primaries and intermediates

The preparation of different primaries and intermediates required for the synthesis of designed nitrogen-containing heterocycles will be achieved by using methodologies reported in the literature as well as by modifying the literature precedents as per the requirements or following green chemistry principles.

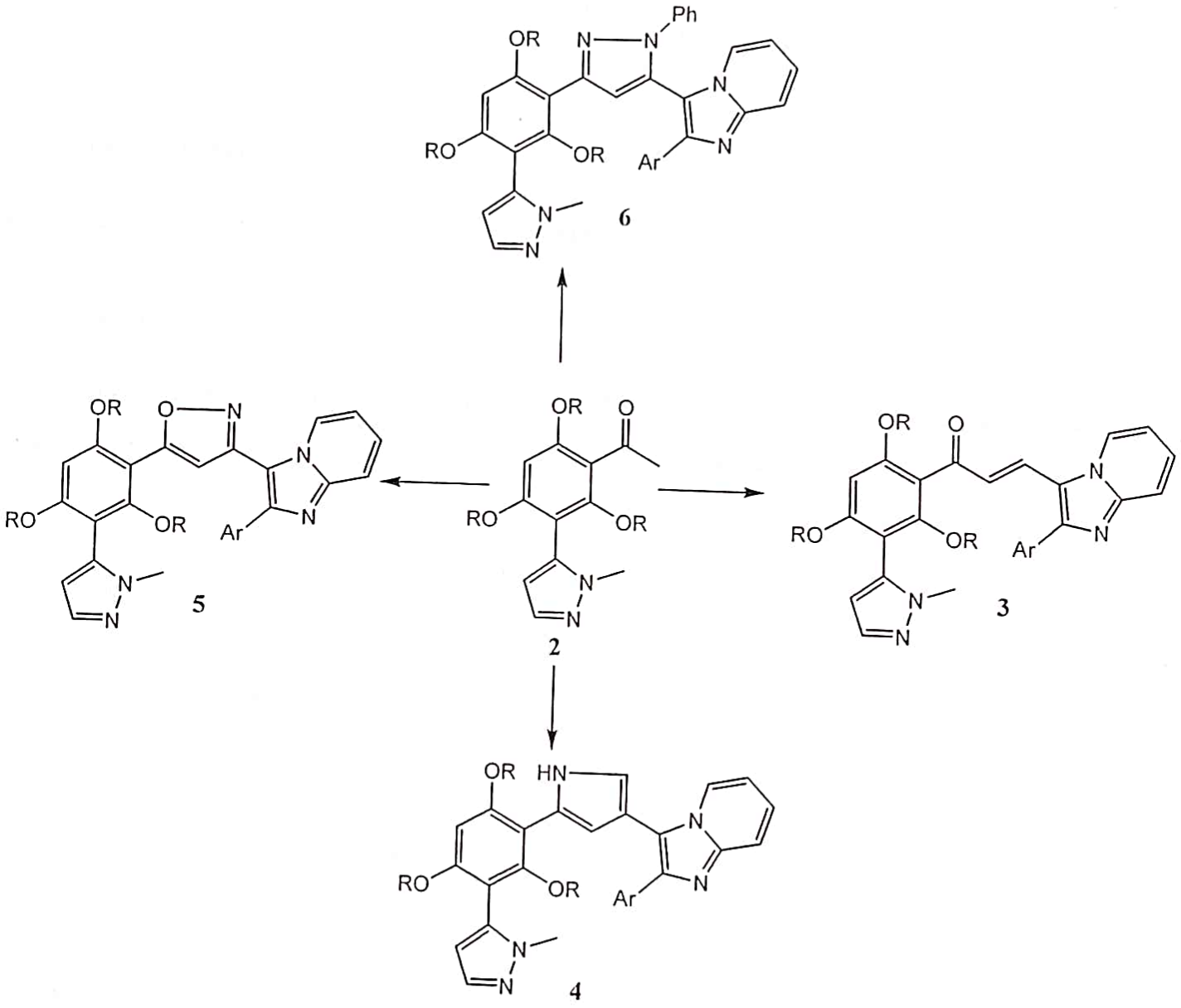
2. Synthesis of target Nitrogen Heterocycles

The synthesis of target Nitrogen-containing bioactive heterocycles will be carried out by employing one-pot, multicomponent strategies, using environmentally friendly catalysts, and employing mild reaction conditions. The reported processes can also be tried as such or with required modifications to improve the yield for the synthesis target compounds.

Some proposed target molecules are listed below (**Scheme 1**):

3. Structural investigations of the synthesized molecules and catalysts

The structures of all the newly synthesized compounds will be confirmed by using different spectroscopic techniques such as UV-Visible, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR X-ray crystallography.



Scheme 1: The proposed Nitrogen-containing heterocycles

4. Biological evaluation of synthesized compounds

All the synthesized compounds will be screened for their therapeutic properties such as anti-inflammatory, anticancer, antioxidants and anti-microbial.

10. Statistical Plan

0-6 Months Synthesis starting materials/substrates	**6-12 Months** Synthesis of the Intermediates	**12-18 Months** Synthesis of the target molecules
18-24 Months Structural investigations and pharmacological evaluation	**24-30 Months** Analysis of data, writing the Research publications & Presentations at Conferences	**30-36 Months** Writing of Synopsis and Thesis for Submission

11. Limitations of the Study

Timely availability of characterization and therapeutic screening facilities.

12. Expected Outcomes of Study

The target molecules designed in the present study will be associated with significant therapeutic properties and can be used as potent leads for the development of novel anti-inflammatory, anti-oxidant and anticancer drugs.

13. Select Bibliography

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